

ANNOTATION

of PhD thesis by Askar Yenglik

on the topic "**Optimizing treatment and conducting a comprehensive diagnosis of chronic endometritis in women experiencing infertility and unsuccessful attempts at assisted reproductive technology (ART), based on the study of endometrial immunohistochemistry markers**", submitted for the degree of Doctor of Philosophy (Ph.D.) in doctoral program **8D10103-«Medicine»**.

Relevance of the problem:

Managing infertility is an important component of sexual and reproductive health. Infertility has devastating social and health consequences, including social stigma, economic hardship, and mental health problems. According to the World Health Organization (WHO), infertility is a disease of the male or female reproductive system, defined by the absence of pregnancy for 12 months with regular unprotected sexual intercourse [1]. Infertility is estimated to affect a large proportion of the world's population, with approximately one in six people experiencing infertility in their lifetime, highlighting the urgent need to increase access to affordable, high-quality infertility services for those in need. Infertility affects about 17.5% of the adult population, that is, approximately every sixth person in the world [2]. In the male reproductive system, infertility is most often caused by problems with sperm release, absent or low sperm count, abnormal morphology and impaired sperm motility. In the female reproductive system, infertility can be caused by a number of abnormalities of the ovaries, uterus, fallopian tubes and endocrine system. The overall prevalence of primary infertility is 9.6% For secondary infertility, the estimated overall prevalence is 6.5% [2]. In Kazakhstan, about 15-17% of married couples suffer from infertility. In the structure, female infertility is 50-60%. There are 26,000 women diagnosed with infertility on the dispensary register [3]. According to ESHRE, on average, 3 cycles of ART are required to give birth to a child. The main reasons for failure of embryo pregnancy and endometrial risk (chronic endometritis and associated impairment of endometrial receptivity) [4].

Uterine factor plays an important role in the genesis of unsuccessful attempts in IVF programs. In recent years, there has been growing interest in chronic endometritis, especially due to its suspected role in infertility, miscarriage and repeated IVF failure [5,6].

Based on different diagnostic methods in the studied population, the prevalence of CE in infertile women varies significantly between studies: from 2.8 to 86.5% [11,12,13].

According to Kitaya et al., (2018), chronic endometritis occurs in 22% of patients in the IVF program, in 14% of unexplained infertility and in 23.6% of women with miscarriages in the first trimester [11,14]. The incidence of infertility in women diagnosed with chronic endometritis is 60 % (22.1% - primary, 36.5% - secondary), 80% of women with chronic endometritis have a history of repeated unsuccessful attempts at assisted reproductive technologies [15,16,17]. According to numerous studies, chronic endometritis is the main verified cause of miscarriage in 47.4-52.1%. [18,19,20,21].

Chronic endometritis is a complex condition with many unresolved problems. To date, there are no recommendations or consensus regarding exactly how to diagnose this condition and how best to treat it [11].

Despite numerous successes and achievements, reproductive medicine has long ignored the endometrial factor. Until 2010, all major research was aimed at studying embryo quality. The last decade marked the start of active research into endometrial implantation factor. Although technology in embryology and embryo transfer has improved significantly over the past 30 years, the success rate of IVF worldwide remains low, with current live birth rates of 25–30%.

The purpose of research: to develop a comprehensive diagnosis and treatment of chronic endometritis in patients with repeated failures in ART programs based on the study of endometrial immunohistochemistry.

Research objectives:

1. To analyze the outcomes of ART programs in women with chronic endometritis, taking into account clinical, laboratory and diagnostic data.
2. Determine the diagnostic value of the content of inflammatory markers (CD138+, CD20+, CD8+) and signaling molecules of endometrial receptivity - receptors for estradiol and progesterone, integrin alpha-V/beta-3 (CD61), leukemia inhibitory factor (LIF) and pinopodia in epithelia endometrium, focusing on the period of the “window of implantation”.
3. To optimize and scientifically substantiate the diagnostic scheme and complex treatment of chronic endometritis in women with infertility and unsuccessful attempts at transfer.
4. Assess the clinical effectiveness of diagnosis and combined treatment of chronic endometritis.

Research methods: A bidirectional cohort study was conducted.

Object of study: women of reproductive age with unsuccessful ART attempts with signs of CE

Subject of study: Endometrium of women with unsuccessful ART attempts with signs of CE

Provisions for defense

1. Chronic endometritis (endometrial factor) is one of the main causes of failure in ART programs. Chronic inflammation of the endometrium causes the release of inflammatory cytokines, which lead to impaired expression of endometrial receptivity signaling molecules during the “window of implantation”.

2. To confirm the diagnosis of chronic endometritis in women with unsuccessful ART programs, the results of an immunohistochemical study of inflammatory response markers CD138+, CD20+, CD8+ should be considered diagnostically significant.

3. Carrying out an immunohistochemical study to evaluate signaling molecules during the “window of implantation”, as a prognostic criterion, can increase the chances of pregnancy after transferring a single high-quality thawed embryo.

4. Carrying out ultrasonic cavitation of the uterine cavity in complex therapy of chronic endometritis increases the effectiveness of the outcomes of ART programs by increasing the frequency of clinical pregnancy and the take home baby rate.

Scientific novelty of the study

For the first time in Kazakhstan, a scientifically based algorithm for the diagnosis and treatment of chronic endometritis in women with infertility and unsuccessful attempts at ART programs was developed.

For the first time in Kazakhstan, in the diagnosis of chronic endometritis in women with repeated implantation failures, a complex diagnosis was used, which included a hysteroscopic examination with an endometrial biopsy and a pathomorphological study, a detailed immunohistochemical study of the endometrium for cells of the immune inflammatory response CD138+, CD20+, CD8+.

For the first time in Kazakhstan, signaling molecules of endometrial receptivity were studied in women with chronic endometritis and repeated failures of ART programs during the “window of implantation” (LIF, pinopodia and estradiol and progesterone receptors).

We were the first to study the cell adhesion molecule integrin alpha-V/beta-3 (CD61) and its role in the implantation process in women with repeated implantation failures and chronic endometritis.

Theoretical and practical outcomes of the PhD work

The study made it possible to develop a fundamentally new algorithm for the diagnosis and treatment of chronic endometritis, the use of which made it possible to increase the frequency of pregnancy and childbirth in women with a history of unsuccessful attempts at transfer.

A scientifically based algorithm for the diagnosis and treatment of chronic endometritis in women with unsuccessful attempts at ART programs has been developed.

An algorithm for the treatment of chronic endometritis in women with repeated implantation failures has been developed and implemented.

2 author's certificates were obtained for methods of diagnosis and treatment of chronic endometritis in women with repeated failures of ART programs.

The author's personal contribution includes the development of the theoretical and methodological program of research, the organization and conduct of the study, direct participation in all stages of research, statistical processing of data, the writing of sections of the thesis, the interpretation and discussion of results, the formulation of defensive statements and conclusions and practical recommendations.

Conclusion:

1. Gynecological history was burdened with inflammatory diseases of the genital organs 58.5%, endometrial and cervical canal polyps 28.7%, endometriosis of various localizations 17.4%, fibroids 10% and ovarian cysts 13%. The obstetric history was aggravated by premature birth, non-developing and ectopic pregnancy, spontaneous miscarriage and medical abortion. In the study groups, the obstetric history was aggravated by premature birth, non-developing and ectopic pregnancy, spontaneous miscarriage and medical abortion.

2. In patients with unsuccessful attempts at ART programs, a pronounced expression of inflammatory markers in the endometrial stroma to CD138+ 10 times, CD20+ 8.5 times, CD8+ 4 times, a revealed decrease in signaling molecules during the “window of implantation” by 3 times (LIF, expression to estradiol receptors in the stroma and glands, progesterone receptors in the stroma and glands, integrin $\alpha V\beta 3$, number of pinopodium).

3. The proposed scheme for complex therapy of chronic endometritis using ultrasonic cavitation of the uterine cavity will allow to successfully stop the inflammatory process, reduce the expression of indicator markers to standard values ($p < 0.05$), increase implantation potential of endometrium during the “implantation window” ($p < 0.05$), increased expression of LIF (3.59 ± 1.53 and 8.05 ± 1.172), estradiol receptors in the stroma (139.7 ± 41.4 and 220.7 ± 58.8) and in the glands (151.9 ± 63.5 and 258 ± 31.7), progesterone receptors in the stroma (131.7 ± 52.8 and 253.9 ± 35.7) and in the glands (111.1 ± 70.8 and 195.0 ± 64.2), integrin $\alpha V\beta 3$ (1.17 ± 0.55 and 3.63 ± 0.52), the verification of mature pinopodium ($p < 0.05$).

4. According to the results of this study, a significant advantage was revealed in the effectiveness of the complex method of treating chronic endometritis with ultrasonic cavitation of the uterine cavity, compared with standard therapy with antibacterial drugs. The effectiveness of treatment was assessed after the transfer of a single thawed embryo of high morphological quality according to Gardner $\geq 4AB$, according to the incidence of clinical pregnancy and their outcomes. The rate of clinical pregnancy per transfer was significantly higher in the group of antibiotic therapy in combination with ultrasonic cavitation of the uterine cavity compared with

the group of standard antibiotic therapy (68.6% vs. 48%; $p < 0.001$.) Accordingly, the rate of live births was significantly higher in the main group. group (60.8% vs. 38%; $p = 0.002$). An integrated approach to the treatment of endometrial inflammatory processes can be recommended for women with reproductive failures caused by chronic endometritis.

Published papers on the topic of the thesis

7 scientific papers have been published on the topic of the dissertation research, including:

1 publication in Scopus CiteScore 3.2, percentile "Obstetrics and Gynecology"

1 publication in the Web of science Core collection. "Problems of Reproduction"

3 publications in a publication recommended by the Committee for Quality Assurance in the Field of Science and Higher Education of the Ministry of Science and Higher Education;

2 theses were published in the collection of a foreign conference;

Approbation of the thesis

The study materials were presented and discussed at the following conferences:

European Society of Human Reproduction and Embryology 37th Annual meeting, 26 June-1 July 2021, «Uterine cavity in patients with repeated implantation failure (RIF) and before the first in vitro fertilization (IVF) program.

European Society of Human Reproduction and Embryology 38th Annual meeting, 3-6 July 2022, «P-373 T657C SYCP3 mutation increases the risk of recurrent miscarriage: a meta-analysis»

XIII International Congress of the Kazakhstan Association of Reproductive Medicine, 4-6 November 2021: Modern paradigms of endometrial research in ART programs

Congress of the Kazakhstan Association of Reproductive Medicine, Symposium "Infections in Reproductive Medicine" June 3, 2023 "The influence of infectious factors on infertility and RIF."

Awards

1. Prize-winner of the "Fertility award" competition, 3rd place, aimed at supporting and developing innovations in the field of reproductive medicine 2022, Antalya, Turkey

2. Prize-winner of the "Fertility award" competition, 2nd place, aimed at supporting and developing innovations in the field of reproductive medicine, 2023, Cannes, France

The scope and structure of the thesis.

The dissertation work is set out on 100 pages, the structure contains an introduction, 3 sections of the main chapters, a conclusion which sets out the main conclusions, practical recommendations and a list of references. There are 146 literary sources in the thesis, 10 diagrams, 25 tables and 17 figures.